ORIGINAL ARTICLES

Heterogeneity of anti-PR3 associated disease in Hong Kong

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Abstract

Thirty seven patients tested positive for antibody against proteinase 3 (anti-PR3) using either one of the two in-house ELISA methods at the Immunology Laboratory, University of Hong Kong. All except three were Chinese. Systemic vasculitis was diagnosed in 13 patients. However, the positive predictive value of anti-PR3 for Wegener's granulomatosus was low (22%). The commonest presenting feature was respiratory (32%). Both respiratory and renal symptoms were commonly reported in anti-PR3 positive patients as in previous studies. In this largely Chinese population, there is marked variability in the spectrum of diseases associated with anti-PR3; though many had vasculitic diseases, some were diagnosed with other conditions such as inflammatory bowel diseases and respiratory infection. In contrast with series in white people, antimyeloperoxidase rather than anti-PR3 associated disease is more prevalent in Chinese patients.

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The association of antineutrophil cytoplasm antibody (ANCA) with systemic vasculitis has been well proved over the last decade.[1][2] Two broad groups of ANCA are now recognised: cytoplasmic (cANCA) and perinuclear (pANCA) forms, distinguished by their respective patterns on indirect immunofluorescence. The major autoantigen for cANCA is proteinase 3 (PR3) whereas that for pANCA is myeloperoxidase (MPO). Anti-PR3 is strongly associated with active Wegener's granulomatosus.[3] The prevalence of different forms of ANCA varies from one locality to another but clinical research on ANCA so far has been focused on white communities. We set out to examine the clinical correlation of anti-PR3 in Hong Kong, where there is a predominantly Chinese population.

Methods

Over a 15 month period (November 1995 to January 1997) all blood samples submitted to the Immunology Laboratory of the Queen Mary Hospital, Hong Kong, for ANCA assays, were screened for anti-PR3 by indirect immunofluorescence and enzyme linked immunosorbent assay (ELISA). Two ELISA test systems were used, one based on the direct binding of antibody to immobilised PR3, and the other on the capture of the antigen by a monoclonal antibody. In each assay a standard curve was prepared by serial dilution of an international standard serum; ELISA results were expressed as a percentage of the standard. Demographics and clinical data of patients tested positive for anti-PR3 by one or both methods were analysed, using a standard questionnaire issued to attending physicians.

Clinical data from 37 anti-PR3 positive patients were obtained for analysis. The mean age was 53 years. All except three were ethnic Chinese, and 22 were men. Systemic vasculitis was the diagnosis in 13 cases, and a further six had renal limited diseases. Assuming that renal diseases were due to vasculitis, the overall predictive value of anti-PR3 for vasculitis was 51%. Wegener's granulomatosus was diagnosed (using the American College of Rheumatology 1990 classification criteria) only in four men and four women. Interestingly, six (27%) of the male patients but no females were given a primary diagnosis of renal disease, the latter was possibly related to the underlying vasculitic process. Six women had a miscellaneous diagnosis not classifiable in any broad group—livedo reticularis (1), primary

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Table 1 Organ system involvement of anti-PR3 positive patients (n=37)

	No (%)*
Lung	18 (49)
Kidney	16 (43)
Upper respiratory tract	8 (22)
Skin	7 (19)
Gastrointestinal tract	5 (14)
Neurological system	4 (11)
Joints	4 (11)
Eye	3 (8)
(Unexplained fever)	3 (8)

*Some patients had more than one system/organ involved.

Table 2 Initial presentation of anti-PR3 positive patients (n=37)

	No (%)*
Lower respiratory (for example, cough, haemoptysis)	12 (32)
Renal (for example, renal insufficiency, proteinuria)	5 (14)
Gastrointestinal	4 (11)
Upper respiratory	3 (8)
Cutaneous vasculitis	3 (8)
Joint pain	3 (8)
Systemic upset (for example, fever)	3 (8)
Eye (for example, scleritis)	3 (8)
Cardiovascular (for example, heart failure)	2 (5)

*Some patients had more than one initial symptom.

amyloidosis (1), relapsing polychondritis (1), mononeuropathy (1), and unclassified (2).

The spectra of clinical presentation and organ system involvement are shown in tables 1 and 2, which are similar to other published series.[2] The commonest initial presenting feature was respiratory, reported in 12 (32%) of all patients. The symptoms were commonly cough, haemoptysis, and/or shortness of breath. Eighteen (49%) had respiratory symptoms sometime in the course of their illnesses. Seven patients had pulmonary disease as their major clinical diagnosis—pneumonia (3), bronchiectasis (2), pulmonary fibrosis (1), and unexplained lung shadows (1). Upper respiratory tract symptoms were the initial presentations in three patients but were seen in eight during the entire follow up period. A total of 16 had features referable to the renal system—proteinuria (11), renal failure (8), urinary casts (2), and haematuria (1). Seven had renal biopsy performed; three of which showed crescentic glomerulonephritis. Other clinical manifestations reported were those of skin, joints, eyes, and the gastrointestinal system. Of note were three men who had inflammatory bowel disease proved on biopsy.

Discussion

cANCA has long been considered a useful marker of Wegener's granulomatosus. The sensitivity of anti-PR3 in the diagnosis of Wegener's granulomatosus was reported to range from 75% to 90%, whereas its specificity could be as high as 98%.[3] In our series, however, the positive predictive value of anti-PR3 for Wegener's granulomatosus is only 22%. To further examine the incidence of ANCA associated diseases, we reviewed our laboratory's data for the 18 month period from January 1996 to June 1997. In this supplementary study, 45 patients tested positive for antimyeloperoxidase (anti-MPO) and 32 for anti-PR3. The anti-MPO: anti-PR3 ratio was 1.4:1. This appears to be the reverse of the situation in white populations which showed a higher rate of anti-PR3 associated Wegener's granulomatosus than anti-MPO associated microscopic polyarteritis.[4][5] It is clear from our study, therefore, that anti-PR3 is rarer than anti-MPO in the Chinese, and the positive predictive value of anti-PR3 for Wegener's granulomatosus is very low. This phenomenon reflects the very low incidence of Wegener's granulomatosus in the Chinese. In Hong Kong we estimate it to be no more than two per million per annum.

Systemic vasculitis is known to be an uncommon condition. Though anti-PR3 is often considered a diagnostic marker of Wegener's granulomatosus, our observation suggests that there is much variability in the disease spectrum associated with the antibody in Chinese patients. A majority of our anti-PR3 positive patients have some forms of vasculitic disease, while a significant proportion is linked with other conditions like inflammatory bowel diseases and respiratory infections. Whereas the detection of a positive anti-PR3 result in a white person may easily lead to a diagnosis of Wegener's granulomatosus, its relevance in Chinese patients must be treated with caution as the diagnosis is largely a clinicopathological one. In conclusion, the testing for cANCA and anti-PR3 can provide useful supplementary information to support a diagnosis of Wegener's granulomatosus, but should never be treated as a diagnostic procedure by itself.

1 Van der woude FJ, Rasmussen N, Labatto S, *et al.* Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosus. *Lancet* 1985;**i**:425–7.
2 Jennette JC, Falk RJ. Small vessel vasculitis. *N Engl J Med* 1997;**337**:1512–23.
3 Kallenberg CGM, Brouwen E, Weening JJ, *et al.* Antineutrophil cytoplasmic antibodies: current diagnostic and pathophysiological potential. *Kidney Int* 1994;**46**:1–15.
4 Watt RA, Carruthers DM, Scott DGI. Epidemiology of systemic vasculitis: changing incidence or definition. *Semin Arthritis Rheum* 1995;**25**:28–34.
5 Lee SS, Lawton JWM. Antimyeloperoxidase antibody in Chinese patients in Hong Kong: a five year review. *Hong Kong Medical Journal* 1996;**2**:40–6.